2008 new drug approvals

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This article provides a brief review of selected new drug entities approved by the Food and Drug Administration (FDA) in 2008.

ALVIMOPAN (ENTEREG)

Therapeutic use: Alvimopan (1–3) is a peripherally acting, selective mu-opioid receptor antagonist with no detectable opioid-agonistic effects. It is indicated to hasten the recovery of the upper and lower gastrointestinal tract after partial small or large bowel resection surgery with primary anastomosis. Clinical trials have demonstrated that use of alvimopan results in reductions in the median time to first flatus passage, time to first bowel movement, time to ready for discharge, time to solids consumption, and time to actual hospital discharge; however, not all trials have shown consistent results. Decreased rates of vomiting, nausea, and overall incidence of gastrointestinal adverse effects have also been noted.

Recommended dosage: Adult inpatients should receive 12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharge. The number of total doses administered should not exceed 15. Alvimopan is supplied in 12-mg capsules.

Drug interactions: In vitro drug interaction studies have not shown a pharmacokinetic effect on alvimopan or concomitantly administered drugs.

Black box warning: Alvimopan is available only for short-term use (15 doses) in hospitalized patients. To obtain alvimopan, hospitals must register with the Entereg Access Support and Education (E.A.S.E.) program.

Adverse reactions: Effects most commonly associated with the use of alvimopan in bowel resection patients include anemia (5.2%), constipation (4%), dyspepsia (7%), hypokalemia (9.5%), back pain (3.3%), and urinary retention (3.2%). The E.A.S.E. program is a result of safety data from a long-term trial of patients with opioid-induced bowel dysfunction. An increased number of myocardial infarctions occurred in the alvimopan group compared with the placebo group (7/538 vs 0/267, not significant).

BENDAMUSTINE HYDROCHLORIDE (TREANDA)

Therapeutic use: Bendamustine (4) is an alkylating agent that binds interstrand DNA, resulting in cell death; it is active against quiescent and dividing cells. Its FDA-approved indications include treatment of chronic lymphocytic leukemia and indolent B-cell non-Hodgkin's lymphoma progressing during or within 6 months of therapy with rituximab regimens.

Recommended dosage: The recommended adult dosage for chronic lymphocytic leukemia is 100 mg/m^2 given intravenously over 30 minutes on days 1 and 2 of a 28-day cycle for a maximum of six cycles. To treat non-Hodgkin's lymphoma in adults, bendamustine 120 mg/m^2 should be administered intravenously over 60 minutes on days 1 and 2 of a 21-day cycle for a maximum of eight cycles. Dose adjustments and/or delays should be considered if significant toxicity is evident. Formal assessments of the use of bendamustine in renal or hepatic impairment have not been performed. However, the manufacturer recommends cautious use in patients with mild to moderate renal dysfunction and avoidance of use in patients with a creatinine clearance (CrCl) <40 mL/min. Additionally, caution is advised when bendamustine is used in patients with mild hepatic dysfunction, and use in patients with moderate or severe hepatic dysfunction should be avoided. Bendamustine is available as a 100-mg single-use vial.

Drug interactions: No formal drug-drug interaction assessments have been performed. Bendamustine is a cytochrome P450 isoenzyme 1A2 (CYP1A2) substrate, and metabolism via CYP1A2 results in the formation of two active metabolites, gamma-hydroxy bendamustine and N-desmethyl-bendamustine. Caution should be used when administering bendamustine with CYP1A2 inducers (e.g., omeprazole) or inhibitors (e.g., fluvoxamine, ciprofloxacin).

Adverse reactions: Hematologic toxicities include lymphopenia, thrombocytopenia, anemia, neutropenia, and leukopenia (≥15%). Nausea, vomiting, and fever (≥15%) are the most frequently observed nonhematologic adverse reactions.

C1 INHIBITOR, HUMAN (CINRYZE)

Therapeutic use: Cinryze (5–8) is a serine proteinase inhibitor, specifically a C1 inhibitor, found naturally in human blood.

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Cinryze acts as an activation regulator of the complement and intrinsic coagulation pathways and a regulator of the fibrinolytic system. It is indicated for the prevention of angioedema attacks in adolescent and adult patients with hereditary angioedema. Achieving normal concentrations of C1 inhibitor in these patients is believed to prevent attacks of angioedema via modulation of vascular permeability through regulation of the intrinsic coagulation pathway. Impeded androgens (e.g., danazol) and antifibrinolytics (e.g., ε-aminocaproic acid) have been used for chronic therapy to prevent acute attacks; however, the side effect profile and patient response limits their use. Cinryze expands the options for angioedema prophylaxis in patients with hereditary angioedema.

Recommended dosage: The recommended dose in adolescents and adults is 1000 units every 3 to 4 days administered intravenously at a rate of 1 mL/min. Cinryze is available as a 500-unit single-dose vial.

Drug interactions: Studies evaluating drug interactions with Cinryze have not been conducted.

Adverse reactions: Upper respiratory tract infections, sinusitis, rash, and headache (≥5%) are the most frequent adverse reactions noted with Cinryze; thrombotic events have been observed when using higher-than-indicated doses. Because Cinryze is prepared from human plasma, patients are introduced to the risk of infectious pathogen transmission.

Other comments: Unreconstituted vials should be protected from light.

CERTOLIZUMAB PEGOL (CIMZIA)

Therapeutic use: Certolizumab (9, 10) is an inhibitor of tumor necrosis factor alpha (TNFα), a proinflammatory cytokine, and is indicated for use in adult patients to decrease the signs and symptoms of Crohn's disease and maintain clinical response for patients with moderately to severely active disease and inadequate response to conventional therapy. Clinical trials have demonstrated certolizumab's efficacy via the achievement of clinical response and remission (defined as a ≥100-point decline in the Crohn's Disease Activity Index compared with baseline and an absolute score of ≤150, respectively) in patients at week 6 and 26 of therapy. A meta-analysis evaluating placebo-controlled trials of TNFα antagonists concluded that certolizumab had efficacy comparable to that of other TNFα antagonists in the treatment of luminal Crohn's disease; however, its use in fistulizing Crohn's disease requires further investigation.

Recommended dosage: The recommended adult dose is 400 mg given as two 200-mg subcutaneous injections at weeks 0, 2, and 4 followed by 400 mg every 4 weeks if clinical response is achieved with initial doses. Certolizumab is supplied in single-use vials containing 200 mg of lyophilized powder for reconstitution.

Drug interactions: No formal drug-drug interactions have been performed; however, concurrent use of another TNFα antagonist and anakinra led to an increased risk of severe infections and neutropenia with no added benefit. Similar toxicities may be seen when anakinra is used concurrently with certolizumab. Live vaccines should not be used concurrently with certolizumab. Lastly, certolizumab has been noted to interfere with certain coagulation assays, causing elevated activated partial thromboplastin time assay results in patients without coagulation abnormalities.

Black box warning: Opportunistic infections, including tuberculosis and invasive fungal infections, have occurred with the use of certolizumab. Patients should be tested for latent tuberculosis; if positive, treatment for tuberculosis should be started prior to the use of certolizumab. Furthermore, all patients should be monitored for active tuberculosis during treatment regardless of initial tuberculin skin test results.

Adverse reactions: A variety of warnings and precautions (e.g., occurrence of serious infection, tuberculosis, hepatitis B virus reactivation, malignancies, hypersensitivity reactions, neurological reactions, hematological reactions, worsening heart failure, autoimmunity, and immunosuppression) associated with the use of TNFα blockers exist. Common adverse effects reported with therapy include upper respiratory infection, urinary tract infection, and arthralgia (>5%).

CICLESONIDE (ALVESCO)

Therapeutic use: Ciclesonide (11–13) is an inhaled corticosteroid indicated for maintenance therapy of asthma in patients 12 years and older. It is unique in its class because it is formulated as a prodrug that is converted into an active entity in the lungs; thus, ciclesonide has been shown to cause minimal adrenal suppression and related adverse reactions compared with other inhaled corticosteroids. Inhaled corticosteroids have been shown to be the most effective maintenance treatment of asthma; they should not be used for treating acute asthma exacerbations.

Recommended dosage: In patients who have used only bronchodilators, the initial recommended dosage is 80 mcg inhaled twice daily with a maximum of 160 mcg twice daily; in patients who have used inhaled corticosteroids, the initial recommended dosage is 80 mcg inhaled twice daily with a maximum of 320 mcg twice daily. Patients who have used oral corticosteroids should be initiated at the maximum dosage of 320 mcg inhaled twice daily with a gradual reduction in oral corticosteroid dose. Ciclesonide is available as an 80-mcg and a 160-mcg per actuation aerosol inhaler.

Drug interactions: The bioavailability of the active metabolite des-ciclesonide was increased by 3.6-fold after administration of oral ketoconazole, a potent CYP3A4 inhibitor. No drug interactions were noted when ciclesonide was administered concomitantly with albuterol or formoterol.

Adverse reactions: The most frequent adverse reactions observed include headache, nasopharyngitis, sinusitis, pharyngolaryngeal pain, upper respiratory infections, arthralgia, nasal congestion, and pain in extremities or back. Adverse reactions associated with systemic corticosteroids (e.g., immunosuppression, increased risk of infections, hypercorticism, adrenal suppression, growth rate reduction, glaucoma, and cataracts) may be seen in patients using ciclesonide; however, systemic exposure is reduced due to decreased absorption of the drug.

CLEVIDIPINE (CLEVIPREX)

Therapeutic use: Clevidipine (14–19) is an intravenous dihydropyridine L-type calcium channel blocker that decreases peripheral vascular resistance without reducing cardiac filling pressure. It is indicated for the treatment of hypertension when oral therapy is not feasible or desirable. Clinical trials have shown that clevidipine is effective at controlling blood pressure in severe postoperative hypertension. Additionally, clevidipine has been shown to be as effective as nitroprusside in the control of blood pressure with little effect on the heart rate. The rapid onset (2–4 minutes), short duration (5–15 minutes), and low potential for drug interactions seen with clevidipine provide advantages over most of the current treatments; however, its benefit over nicardipine remains unclear.

Recommended dosage: Initial infusion should be administered at 1 to 2 mg/h continuously titrated to the desired blood pressure reduction by doubling the dose at 90-second intervals or 5- to 10-minute intervals as the target blood pressure is approached. An approximate reduction of 2 to 4 mm Hg in blood pressure may be expected with each increase. The maintenance dose for most patients is between 4 and 6 mg/h up to a maximum of 32 mg/h for patients with severe hypertension. Due to lipid load restrictions, a maximum dose of 1000 mL or an average infusion rate of 21 mg/h should not be exceeded in 24 hours. Clevidipine is supplied in 50- and 100-mL single-use vials at a concentration of 0.5 mg/mL.

Drug interactions: No clinical drug interaction studies have been performed. The potential for interaction is believed to be low since neither clevidipine nor its major active metabolite are inhibitors or inducers of the cytochrome P450 system.

Adverse reactions: The most common adverse reactions are headache, nausea, and vomiting (>2%). Less common adverse reactions in patients with severe or essential hypertension include myocardial infarction, cardiac arrest, syncope, and dyspnea (<1%). Additionally, clevidipine use may result in systemic hypotension and reflex tachycardia.

Other comments: Clevidipine is contraindicated in patients with allergies to soybeans, soy products, eggs, or egg products. It should also not be used in patients with defective lipid metabolism or severe aortic stenosis.

DIFLUPREDNATE (DUREZOL)

Therapeutic use: Difluprednate (20, 21) is a topical corticosteroid indicated to decrease inflammation and pain related to ocular surgery. Since sorbic acid is used instead of benzalkonium chloride as a preservative, difluprednate creates less irritation or damage to eye tissues than other ophthalmic steroids available in the United States.

Recommended dosage: Beginning 24 hours after surgery, 1 drop of difluprednate should be instilled into the conjunctival sac of the affected eye(s) 4 times daily for 2 weeks. Then 1 drop should be instilled twice daily for 1 week, with administration tapering off based on response thereafter. Difluprednate is available as a 0.05% ophthalmic emulsion in a 5-mL bottle.

Drug interactions: No formal drug-drug, drug-food, or drug-herb interaction studies have been performed.

Adverse reactions: The most common adverse reactions include corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis (5%–15%). Potentially serious adverse reactions that may occur include intraocular pressure elevation, cataract formation, and ocular infections.

Other comments: Bottles should be protected from light and stored in their protective carton while not in use. Patients should not wear contact lenses while being treated with difluprednate.

ELTROMBOPAG (PROMACTA)

Therapeutic use: Eltrombopag (22, 23) is an orally bioavailable, small molecule, thrombopoietin receptor agonist. It is indicated to treat increased risk of bleeding in patients due to thrombocytopenia resulting from chronic immune thrombocytopenic purpura that is not sufficiently responsive to corticosteroids, immunoglobulins, or splenectomy. Clinical trials have demonstrated that eltrombopag is effective in achieving platelet counts $\geq 50 \times 10^9$/L in patients with initial platelet counts $< 30 \times 10^9$/L.

Recommended dosage: The recommended starting dose in most patients is 50 mg daily to be administered on an empty stomach and with a minimum 4-hour interval between its administration and that of concomitant treatments containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, zinc). A lower dosage of 25 mg daily should be used in patients with moderate to severe hepatic insufficiency and in patients of East Asian descent. Dose adjustments should be made to achieve and maintain platelet levels $\geq 50 \times 10^9$/L. The maximum daily dose is 75 mg daily.

Drug interactions: Eltrombopag is believed to be metabolized by CYP1A2, CYP2C8, UGT1A1, and UGT1A3. Since formal studies have not been performed, caution should be used when administering eltrombopag concomitantly with moderate or strong inhibitors of these enzymes. In vitro studies have also demonstrated that eltrombopag is an inhibitor of OATP1B1 and a variety of uridine 5′-diphospho-glucuronosyltransferases; patients receiving medications that are metabolized through any of these pathways should be monitored for excessive drug exposure.

Black box warning: The use of eltrombopag is associated with an increased risk of hepatotoxicity. Alanine aminotransferase, aspartate aminotransferase, and bilirubin levels should be obtained at baseline and monitored every 2 weeks during the dose adjustment phase and monthly thereafter. The medication should be discontinued if alanine aminotransferase levels increase to ≥3 times the upper limit of normal and are progressive, persistent for at least 4 weeks, accompanied by increased bilirubin, or accompanied by clinical symptoms of liver injury or evidence of hepatic decompensation.

Adverse reactions: Reactions occurring in more than 1% of patients receiving eltrombopag and at a higher rate than placebo include nausea, vomiting, menorrhagia, myologia, paresthesia, cataract formation, dyspepsia, ecchymosis, thrombocytopenia,

elevated alanine aminotransferase and aspartate aminotransferase, and conjunctival hemorrhage. Potential serious effects to monitor include bone marrow reticulin formation and bone marrow fibrosis, thrombotic/thromboembolic complications, and malignancy formation/progression.

Other comments: Prescribers, pharmacies, and patients must be enrolled in the PROMACTA *CARES* distribution program in order to use eltrombopag.

ETRAVIRINE (INTELENCE)

Therapeutic use: Etravirine (24) is a nonnucleoside reverse transcriptase inhibitor indicated for combination antiretroviral treatment of HIV-1 infection with other antiretroviral medications in treatment-experienced patients with proven resistance to other antiretroviral agents. Clinical trials have demonstrated that etravirine produces improved suppression of viral load in treatment-experienced patients infected with HIV-1 compared with placebo.

Recommended dosage: The recommended dosage for treatment-experienced adult patients is 200 mg orally two times daily after meals. Patients unable to swallow the tablets can disperse them in a glass of water. Etravirine is available as 100-mg tablets.

Drug interactions: Since etravirine is a substrate of CYP3A4, CYP2C9, and CYP2C19, an inducer of CYP3A4, and an inhibitor of CYP2C9 and CYP2C19, caution should be used when administering it with other CYP3A4, CYP2C9, and/or CYP2C19 inducers, inhibitors, or substrates. Concurrent use of etravirine with tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, protease inhibitors without ritonavir, and nonnucleoside reverse transcriptase inhibitors should be avoided.

Adverse reactions: Rash and nausea (>10%) are the most frequent adverse reactions observed in patients using etravirine. Rarely, life-threatening skin reactions and immune reconstitution syndrome have been reported.

FESOTERODINE FUMARATE (TOVIAZ)

Therapeutic use: Fesoterodine (25, 26) is a competitive antagonist of the muscarinic receptor that is formulated as a prodrug. It is indicated for the treatment of overactive bladder presenting with symptoms of urge incontinence, urgency, and frequency. Fesoterodine has been shown to provide improved symptomatic efficacy within 2 weeks of treatment initiation in a dose-dependent manner.

Recommended dosage: The initial recommended dosage is 4 mg orally daily, which may be titrated to 8 mg daily depending on response and tolerability. Patients with severe renal impairment (CrCl <30 mL/min) should not exceed 4 mg daily due to a potential increase in maximum concentration and bioavailability by 2- and 2.3-fold, respectively. In addition, fesoterodine should not be used in patients with severe hepatic impairment, as studies have not been conducted in this patient population. Fesoterodine is available as 4- and 8-mg extended-release tablets.

Drug interactions: A maximum of 4 mg daily is recommended in patients receiving concomitant potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) since fesoterodine is a substrate of the enzyme. Caution should be used when fesoterodine is coadministered with other antimuscarinic agents, as anticholinergic effects may be increased.

Adverse reactions: Dry mouth, constipation, dyspepsia, dry eyes, dysuria, and urinary retention were the most common adverse reactions observed; they occur in a dose-dependent fashion.

Other comments: Use of fesoterodine in patients with underlying urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma is contraindicated.

LACOSAMIDE (VIMPAT)

Therapeutic use: Lacosamide (27, 28) is indicated as add-on therapy for partial-onset seizures in epileptic patients. Although the mechanism of action is unknown, lacosamide is thought to stabilize neuronal membranes and inhibit neuronal firing through augmenting slow inactivation of voltage-gated sodium channels. Clinical studies have demonstrated a reduction in seizure frequency with lacosamide as adjunctive therapy in adult patients with refractory epilepsy.

Recommended dosage: The initial dose is 50 mg orally or intravenously 2 times daily. The dose should then be titrated weekly by 100 mg daily up to a recommended maximum of 400 mg daily as appropriate based on patient response. In patients with severe renal impairment (CrCl ≤30 mL/min), 300 mg daily is the recommended maximum dose. A supplemental dose of 50% should be administered following hemodialysis since lacosamide is removed with this procedure. A maximum of 300 mg daily is also recommended for patients with mild or moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment; thus, use is not recommended in this patient population. To convert from one dosage form to another, an equivalent dose and frequency should be used due to 100% bioavailability of the tablet formulation. Lacosamide is available as 50-, 100-, 150-, and 200-mg tablets and also as a 200 mg/20 mL single-use vial.

Drug interactions: Clinical studies have not identified any drug-drug interactions associated with lacosamide.

Adverse reactions: Dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and blurred vision were the most frequent adverse reactions observed. Similar to all other antiepileptic medications, lacosamide has the potential to increase the risk of suicidal ideation. In addition, caution should be used in patients with cardiac rhythm or conduction abnormalities or severe cardiac disease, as lacosamide may predispose these patients to cardiac complications.

Other comments: A medication guide explaining the risk of suicidal ideation with antiepileptic drugs is available for patient distribution. Pregnant women using lacosamide are advised to enroll in the UCB Antiepileptic Drugs (AED) Pregnancy Registry and the North American Antiepileptic Drug Pregnancy Registry.

METHYLNALTREXONE BROMIDE (RELISTOR)

Therapeutic use: Functioning as a selective mu-opioid receptor antagonist in peripheral tissues, methylnaltrexone (29, 30)

is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care without adequate laxative response. Due to its chemical structure, methylnaltrexone cannot cross the blood-brain barrier and thus does not affect opioid pain relief. Clinical trials have shown that approximately 50% of patients on methylnaltrexone experienced a laxation response within 4 hours of the first dose and reported less difficulty with laxation and reduced distress associated with constipation.

Recommended dosage: The recommended dose is 8 mg in patients weighing 38 to 61 kg, 12 mg in patients weighing 62 to 114 kg, and 0.15 mg/kg in patients weighing <38 kg or >114 kg. Methylnaltrexone is typically administered once every other day subcutaneously; dosing frequency should not exceed more than 1 dose in a 24-hour period. The dose should be reduced by 50% in patients with severe renal impairment (CrCl <30 mL/min). Methylnaltrexone is available as a 12 mg per 0.6 mL single-use vial.

Drug interactions: Methylnaltrexone is a weak inhibitor of CYP2D6; however, studies have not shown metabolism of CYP2D6 substrates to be significantly affected by methylnaltrexone.

Adverse reactions: The most frequent adverse reactions reported consist of abdominal pain, flatulence, nausea, dizziness, and diarrhea (>5%). Therapy with methylnaltrexone should be discontinued if symptoms of severe or persistent diarrhea occur.

Other comments: In patients with known or suspected mechanical gastrointestinal obstruction, methylnaltrexone treatment is contraindicated. Vials should be protected from light prior to use.

PLERIXAFOR (MOZOBIL)

Therapeutic use: Plerixafor (31) is a CXCR4 chemokine receptor antagonist; CXCR4 is known to play a role in movement of human hematopoietic stem cells to the marrow compartment and their attachment to the matrix. It is indicated for use in non-Hodgkin's lymphoma and multiple myeloma patients preparing for autologous transplantation. Plerixafor in combination with granulocyte-colony stimulating factor (G-CSF) can be used to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent use during transplantation. Clinical trials have demonstrated that patients receiving plerixafor more often collected a minimum of 5×10^6 $CD34^+$ cells/kg and achieved this number more quickly than patients in the placebo group.

Recommended dosage: After a patient has received 4 days of G-CSF and a minimum of 11 hours prior to apheresis, subcutaneous injection of plerixafor at a dose of 0.24 mg/kg up to 40 mg/day for a maximum of 4 days is recommended. Daily G-CSF dosing should continue while the patient is receiving apheresis. Patients with moderate and severe renal impairment (CrCl ≤50 mL/min) should receive a lower dose of 0.16 mg/kg up to a maximum dose of 27 mg/day. Plerixafor is available at a concentration of 20 mg/mL in a 1.2-mL single-use vial.

Drug interactions: No drug-drug interactions have been identified.

Adverse reactions: White blood cell and platelet counts should be monitored during therapy, as use of plerixafor in conjunction with G-CSF can increase circulating leukocytes and result in thrombocytopenia. Also, the manufacturer warns that tumor cells may be released from the marrow with use of plerixafor and subsequently collected in the leukapheresis product. Animal studies have indicated that daily administration of plerixafor may result in splenic enlargement; thus, patients reporting left upper abdominal pain and/or scapular or shoulder pain should be evaluated. Common adverse reactions noted with the use of plerixafor include diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting (≥10%).

ROMIPLOSTIM (NPLATE)

Therapeutic use: Acting as an agonist of the thrombopoietin receptor, romiplostim (32, 33) increases platelet production in the bone marrow. It is indicated for the treatment of chronic immune (idiopathic) thrombocytopenia purpura in patients at an increased risk of bleeding and with an inadequate response to corticosteroids, immunoglobulins, or splenectomy. Clinical trials have demonstrated that platelet counts of $\geq 50 \times 10^9$/L were maintained in patients with refractory chronic immune thrombocytopenia purpura with and without splenectomies.

Recommended dosage: The recommended starting dose is 1 mcg/kg of actual body weight subcutaneously injected weekly to reach a goal platelet count $\geq 50 \times 10^9$/L. The dose may be titrated by 1 mcg/kg weekly until this goal is achieved or a maximum of 10 mcg/kg dose is reached. Use should be discontinued if there is no increase after 4 weeks at the maximum dose. Romiplostim is available as 250- and 500-mcg single-use vials.

Drug interactions: Formal drug interaction studies with romiplostim have not been conducted.

Adverse reactions: The most frequent adverse reactions observed with romiplostim include arthralgia, dizziness, insomnia, myalgia, dyspepsia, paresthesia, and extremity, abdominal, and shoulder pain (>5%). Rarely, bone marrow reticulin development, thrombotic or thromboembolic complications, and hematologic malignancies have been reported with romiplostim. In addition, decreases in platelet levels have been reported upon discontinuation of romiplostim.

Other comments: Prescribers and patients must be enrolled in the Nplate Network of Experts Understanding and Supporting Nplate and Patients (NEXUS) Program to prescribe, administer, and receive romiplostim.

RUFINAMIDE (BANZEL)

Therapeutic use: Rufinamide (34, 35) is an antiepileptic that is believed to delay sodium channel recovery; it is indicated for adjunct treatment of seizures associated with Lennox-Gastaut syndrome in patients at least 4 years old. One clinical trial demonstrated that rufinamide reduced seizure frequency and severity and improved the Seizure Severity Rating from Global Evaluation when compared with placebo.

Recommended dosage: For adults, the initial dosage should be 200 to 400 mg twice daily increased by 200 to 400 mg per dose every 2 days until the target dose of 1600 mg twice daily

is reached. For children at least 4 years old, the initial dosage should be 5 mg/kg twice daily increased by 5 mg/kg per dose every other day until the lesser of 22.5 mg/kg or 1600 mg twice daily is reached. Doses should be administered with food. Rufinamide is supplied in 200- and 400-mg tablets.

Drug interactions: Pharmacokinetic studies have noted the following interactions: 1) rufinamide reduced carbamazepine and lamotrigine concentrations and increased phenytoin and phenobarbital concentrations; 2) phenytoin, phenobarbital, and primidone reduced rufinamide concentrations; 3) carbamazepine dose-dependently reduced rufinamide concentrations; and 4) valproate dose-dependently increased rufinamide concentrations. These effects were not noted to be of significance for most patients; however, pediatric patients may be more susceptible to larger variations. Caution should be used in patients on multiple antiepileptic drugs, specifically valproate, and lower doses should be utilized when appropriate. Furthermore, rufinamide reduced the bioavailability and maximum concentration of hormonal contraceptives with unknown clinical effects; patients should be advised to utilize another method of contraception.

Adverse reactions: Effects commonly associated with therapy include drowsiness, fatigue, dizziness, ataxia and gait disturbance, nystagmus, vision disturbances, nasopharyngitis, headache, nausea, vomiting, tremor, and convulsion (≥3%), and those most commonly leading to treatment discontinuation included convulsions, rash, fatigue, vomiting, dizziness, headache, nausea, and ataxia. Additionally, the manufacturer warned of the risk of QT-interval shortening with the use of rufinamide. Patients with familial short QT syndrome should not be treated with this medication, and caution should be used when administering it concomitantly with other drugs that shorten the QT interval.

Other comments: A medication guide explaining the risk of suicidal ideation with antiepileptic drugs is available for patient distribution.

SOMATROPIN (ACCRETROPIN)

Therapeutic use: Somatropin (36) is a recombinant protein (from *Escherichia coli* fermentation) that is chemically and physicochemically identical to human pituitary growth hormone (GH). It is indicated for the treatment of pediatric patients with growth failure due to inadequate GH secretion and short stature associated with Turner syndrome in patients whose epiphyses are not closed. Clinical trials in patients with GH deficiency have demonstrated that the use of somatropin resulted in a mean height increase of 8.88 cm, 7.64 cm, and 6.98 cm per year after the first, second, and third year of use, respectively. In patients with Turner syndrome, increases were 8.56 cm, 6.85 cm, and 5.84 cm, respectively.

Recommended dosage: Dosing should be individualized, and therapy should not continue once epiphyseal fusion occurs. The weekly recommended dosage for treatment of GH deficiency is 0.18 mg/kg to 0.3 mg/kg subcutaneously divided into 6 to 7 daily doses, while the recommendation for Turner syndrome is 0.36 mg/kg weekly given subcutaneously in 6 to 7 daily doses. Somatropin is supplied in multidose vials.

Drug interactions: Somatropin inhibits 11β-hydroxysteroid dehydrogenase type 1, which can significantly alter the metabolism of cortisone and cortisol and uncover undiagnosed central hypoadrenalism. Additionally, patients treated for hypoadrenalism with glucocorticoid therapy may require an increased dose when somatropin is added to their regimen. Somatropin may increase clearance of compounds metabolized by CYP isoenzymes; however, no formal drug interaction studies are available.

Adverse reactions: Injection site reactions such as bruising, erythema, hemorrhage, edema, pain, pruritus, rash, and swelling have been reported in 50% of patients during clinical study. Other frequent adverse effects include nausea, headache, fatigue, and scoliosis (>3%). Anti-GH antibody may develop but usually in an amount below the threshold that would decrease growth velocity.

Other comments: Multidose vials, once punctured, can be stored in the refrigerator for a maximum of 14 days and should be protected from light.

TETRABENAZINE (XENAZINE)

Therapeutic use: Tetrabenazine (37, 38) depletes central monoamines via reversible binding to the human vesicular monoamine transporter type 2. It is indicated for the treatment of chorea associated with Huntington's disease. Clinical trials have demonstrated tetrabenazine's effectiveness in the reduction of Total Chorea Score and improvement in Clinical Global Impression.

Recommended dosage: The initial recommended dose is 12.5 mg once daily with weekly titrations in 12.5-mg intervals. Daily dosages should be divided in two to three divided doses, with a single maximum dose of 25 mg. The dose should be titrated based on patient response; patients requiring doses >50 mg should be genotyped for CYP2D6 activity. Patients identified as extensive or intermediate metabolizers may receive single doses up to 37.5 mg with maximum daily doses of 100 mg. Tetrabenazine is contraindicated in patients with liver disease. Tablets are available in strengths of 12.5 and 25 mg.

Drug interactions: Due to its metabolism via CYP2D6, coadministration of tetrabenazine with strong CYP2D6 inhibitors may increase its effect; patients stabilized on tetrabenazine should have their dose halved. Reserpine and tetrabenazine should not be used together, and caution should be used when changing from one product to the other to avoid overdosage. A 20-day washout period is recommended.

Black box warning: Use of tetrabenazine may increase a patient's risk of depression and suicidal thoughts and behavior. Patients should be informed of the risk, and health care professionals should monitor patients during tetrabenazine treatment.

Adverse reactions: Common effects associated with therapy include sedation (31%), fatigue (22%), insomnia (22%), depression (19%), akathisia (19%), and nausea (13%). The following serious effects may occur: neuroleptic malignant syndrome, Parkinsonism, QT-interval prolongation, hyperprolactinemia, and tardive dyskinesia.

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